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CLINICAL THERAPEUTICS

Elevated Plasma Moxifloxacin Concentrations and *SLCO1B1* g.−11187G>A Polymorphism in Adults with Pulmonary Tuberculosis

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ABSTRACT Moxifloxacin exhibits concentration-dependent prolongation of human QTc intervals and bactericidal activity against *Mycobacterium tuberculosis*. However, moxifloxacin plasma concentrations are variable between patients. We evaluated whether human gene polymorphisms affect moxifloxacin plasma concentrations in tuberculosis patients from two geographic regions. We enrolled a convenience sample of 49 adults with drug-sensitive pulmonary tuberculosis from Africa and the United States enrolled in two treatment trials of moxifloxacin as part of multidrug therapy. Pharmacokinetic parameters were evaluated by noncompartmental techniques. Human single-nucleotide polymorphisms of transporter genes were evaluated by analysis of covariance (ANCOVA) on moxifloxacin exposure and the peak (maximum) concentration (C_{max}). The moxifloxacin area under the concentration-time curve from 0 to 24 h (AUC_{0-24}) and C_{max} were significantly increased by the drug milligram-per-kilogram dosage and the genotype of variant g.−11187G>A in the *SLCO1B1* gene (rs4149015) but not by geographic region. The median moxifloxacin AUC_{0-24} was 46% higher and the median C_{max} was 30% higher in 4 (8%) participants who had the *SLCO1B1* g.−11187 AG genotype than in 45 participants who had the wild-type GG genotype (median AUC_{0-24} from the model, 34.4 versus 23.6 μg · h/ml [$P = 0.005$, ANCOVA]; median C_{max} from the model, 3.5 versus 2.7 μg/ml [$P = 0.009$, ANCOVA]). Because moxifloxacin exhibits concentration-dependent prolongation of human QTc intervals and prolonged QTc intervals are associated with cardiac arrhythmia, further study is needed to evaluate the risk associated with the *SLCO1B1* g.−11187G>A variant. (This study has been registered at ClinicalTrials.gov under identifier NCT00164463.)

KEYWORDS antibacterial, pharmacokinetics, pharmacogenetics, fluoroquinolones

Moxifloxacin is a mycobactericidal drug with exposure and concentration-dependent activity (1, 2). Due to its potential sterilizing activity, it is being evaluated as a component in clinical trials of shortening of tuberculosis (TB) treatment (3–5). Moxifloxacin also is recommended for treating patients who have intolerance or resistance to isoniazid and as a component of treatment regimens against multidrug-resistant TB (6).

With a typical 400-mg daily dose, moxifloxacin is considered effective, well tolerated, and safe (7). Notable is the moderate interindividual variability in plasma moxifloxacin

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TABLE 1 Demographic and clinical data from study participants enrolled in TBTC pharmacokinetic studies 27 and 28 who had drug-sensitive tuberculosis and received moxifloxacin coadministered with a rifampin-based multidrug regimen[a]

Characteristic	Values for participants from:			P[b]
	Africa	United States	All	
No. (%) of participants by geographic origin	26 (53)	23 (47)	49 (100)	
No. (%) of participants by race				≤0.001
Black	26 (100)	3 (13)	29 (59)	
White	0 (0)	20 (87)	20 (41)	
Mean ± SD age (yr)	31 ± 8	44 ± 14	37 ± 13	≤0.001
No. (%) of male participants	20 (77)	19 (83)	39 (80)	NS
Mean ± SD wt (kg)	56 ± 9	64 ± 13	60 ± 12	≤0.02
No. (%) of participants with HIV infection	1 (4)	1 (4)	2 (4)	NS
No. (%) of participants with the following cavitation on chest radiograph:				NS
None	9 (35)	5 (22)	14 (29)	
<4 cm total	12 (46)	8 (35)	20 (41)	
≥4 cm total	5 (19)	10 (44)	15 (31)	
Mean ± SD moxifloxacin dose (mg/kg)	7 ± 1	6 ± 1	7 ± 1	≤0.02
Mean ± SD no. of moxifloxacin doses before PK sampling	28 ± 8	22 ± 9	25 ± 9	≤0.02
Mean ± SD rifampin AUC_{0-24} ($\mu g \cdot h/ml$)	42 ± 24	52 ± 29	47 ± 27	NS

[a]Data are for 49 participants. Abbreviations: AUC_{0-24}, area under the concentration-time curve from 0 to 24 h; HIV, human immunodeficiency virus; PK, pharmacokinetic.
[b]*P* values were determined by the chi-square test (categorical variables) or *t* test (continuous variables). NS, not significant ($P > 0.05$).

concentration with oral therapy (8). Caution against the use of larger moxifloxacin daily doses has been advised because of dose-dependent linear increases in placebo-corrected QTc intervals (9). Prolonged QT intervals are associated with torsades de pointes, a potentially fatal ventricular tachyarrhythmia (10, 11).

Predictions about the safety and efficacy of moxifloxacin in individuals are imprecise because of interindividual variability in the peak plasma moxifloxacin concentration and exposure. Genomic variants that affect absorption, transport, metabolism, or excretion may be responsible for the variation in drug concentration between individuals. Moxifloxacin undergoes phase II biotransformation by glucuronide and sulfate conjugations (12). In tuberculosis patients, decreased rifampin concentrations are associated with single-nucleotide polymorphisms (SNPs) in the drug transporter gene *SLCO1B1* (13, 14). The effect of transporter genes had not been carefully studied with moxifloxacin. The purpose of the present study was to determine the effect of genetic variants of the transporter genes *SLCO1B1*, *SLCO1B3*, and *ABCB1* (*MDR1*) on moxifloxacin plasma concentration in adults from two geographic regions who had drug-sensitive tuberculosis and who were enrolled in clinical treatment trials with multidrug therapy.

RESULTS

Study population. Of the 72 participants in the Tuberculosis Trials Consortium (TBTC) pharmacokinetic study 27 and 28 analyses, moxifloxacin pharmacokinetic parameters were evaluated in 49 (68%), including 26 participants (53%) who were enrolled from Africa (Uganda, $n = 24$ [49%]; South Africa, $n = 2$ [4%]) and 23 participants (47%) who were enrolled from the United States. The geographic region of origin was associated with age, race, and weight (Table 1). African participants were an average of 13 years younger and 8 kg lighter than U.S. participants and thus received a higher moxifloxacin mean milligram-per-kilogram dose exposure than U.S. participants because all participants received the same fixed 400-mg dose (Table 1). There were no differences in gender, human immunodeficiency virus coinfection, and the rifampin area under the concentration-time curve (AUC) from 0 to 24 h (AUC_{0-24}) between African and U.S. participants.

Moxifloxacin pharmacokinetics and pharmacogenomics. The moxifloxacin AUC_{0-24} and peak (maximum) concentration (C_{max}) were similar in unadjusted data

TABLE 2 Moxifloxacin pharmacokinetic parameters (unadjusted and AUC_{0-24} adjusted for weight) in univariate analyses in tuberculosis participants from Africa and the United States treated with moxifloxacin coadministered with a rifampin-based multidrug regimen[a]

Pharmacokinetic parameter	No. of subjects	Arithmetic mean ± SD	Geometric mean	P[b]
AUC_{0-24} (μg · h/ml)				NS
All participants	49	25 ± 7	24.2	
Africa	26	27 ± 7	26	
United States	23	24 ± 8	22.4	
C_{max} (μg/ml)				NS
All participants	49	2.8 ± 0.8	2.6	
Africa	26	2.8 ± 0.8	2.7	
United States	23	2.7 ± 0.9	2.6	
Half-life (h)				≤0.04
All participants	49	6 ± 1	6	
Africa	26	6 ± 1	6.3	
United States	23	5.8 ± 0.9	5.7	
AUC_{0-24} per kg (μg · h/ml/kg)				
All participants	49	0.4 ± 0.2	0.4	≤0.04
Africa	26	0.5 ± 0.2	0.5	
United States	23	0.4 ± 0.2	0.4	

[a]Data are for 49 participants. Abbreviations: AUC_{0-24}, area under the concentration-time curve from 0 to 24 h; C_{max}, peak (maximum) concentration.
[b]*P* values were determined by the Wilcoxon rank-sum test. NS, not significant ($P > 0.05$).

between study participants from Africa and the United States (Table 2). The mean AUC_{0-24} adjusted for weight was lower in U.S. participants (Table 2). A higher body weight was associated with a lower AUC_{0-24} and a lower C_{max}, and female gender was associated with a higher AUC_{0-24} (Table 3). The moxifloxacin AUC_{0-24} and C_{max} had interindividual coefficients of variation of about 30% (C_{max}, 30%; AUC_{0-24}, 29%).

Of 49 participants who had moxifloxacin pharmacokinetics and genomic analyses of *SLCO1B1* g.−11187G>A, the AG genotype was identified in 4 (8%) participants, including 1 of black race from Africa and 3 of white race from the United States. Of the 72 participants in studies 27 and 28 with tuberculosis and genomic analysis of *SLCO1B1* g.−11187G>A who either did or did not receive moxifloxacin, 8 (11%) had the AG genotype: 4 (11%) of the 37 participants from Africa of black race and 4 (11%) of 35 participants from the United States. Twenty-nine of the 35 participants from the United States were of white race, and 4 (14%) of the 29 had the *SLCO1B1* g.−11187AG genotype.

For the *SLCO1B1* g.−11187G>A SNP, the median moxifloxacin AUC_{0-24} was 46% higher and the peak concentration was 33% higher in participants with the AG genotype than in those with the wild-type GG genotype (Table 4; Fig. 1). The variables identified by the Bayesian information criterion (BIC) model selection for AUC_{0-24} were weight and gender, and the variable identified by the BIC model selection for C_{max} was weight alone. There were no interactions ($P > 0.05$) between weight and gender for C_{max} or AUC_{0-24}. In the model adjusted for weight and gender, the relative increased effect on AUC_{0-24} was 1.4-fold greater in participants who had the AG genotype (Table 4). The additive effect in the weight-adjusted model on C_{max} was higher in subjects with one A allele than in subjects with two G alleles (Table 4). There were no other significant differences in pharmacokinetic parameters for the other genetic variants tested (Table 4) or for coadministration of isoniazid and/or ethambutol as part of multidrug therapy.

Distribution of *SLCO1B1* single-nucleotide polymorphisms among races and region. The *SLCO1B1* g.−11187GG and -AG genotypes were detected in 45 and 4 participants, respectively. The 29 participants of black race were not more likely than the 20 of white race to have the *SLCO1B1* g.−11187GA genotype associated with higher moxifloxacin concentrations (3% versus 15%; $P = 0.36$, chi-square test) (Table 5).

TABLE 3 Univariate effects of demographics and clinical factors on moxifloxacin pharmacokinetic parameters[a]

Factor	No. of patients	AUC_{0-24}			C_{max}		
		Arithmetic mean ± SD AUC_{0-24} (μg · h/ml)	Geometric mean AUC_{0-24} (μg · h/ml)	*P*[b]	Arithmetic mean ± SD C_{max} (μg/ml)	Geometric mean C_{max} (μg/ml)	*P*[b]
Age (yr) by tertile				NS			NS
18, ≤31	18	28 ± 7	26.7		2.9 ± 0.8	2.8	
>31, ≤38	16	24 ± 5	23.8		2.7 ± 0.7		
>38, 76	15	24 ± 10	22		3 ± 1		
Wt (kg) by tertile				≤0.001			≤0.002
38.2, ≤54.7	17	30 ± 8	28.7		3.3 ± 0.8	3.2	
>54.7, ≤61.2	16	25 ± 5	24.9		2.7 ± 0.7	2.6	
>61.2, 105	16	20 ± 5	19.7		2.3 ± 0.7	2.2	
Gender				≤0.001			NS
Male	39	23 ± 5	22.7		2.6 ± 0.7	2.5	
Female	10	33 ± 10	31.4		3 ± 1	3.1	
Geographic region				NS			NS
Africa	26	27 ± 7	26		2.8 ± 0.8	2.7	
United States	23	24 ± 8	22.4		2.7 ± 0.9	2.6	
Race				NS			NS
Black	29	26 ± 7	25.6		2.8 ± 0.7	2.7	
White	20	24 ± 8	22.4		3 ± 1	2.6	
HIV				NS			NS
No infection	47	25 ± 8	24.3		2.8 ± 0.8	2.6	
Infection	2	23 ± 3	22.7		2.9 ± 0.8	2.9	
Lung cavity at study enrollment				NS			NS
None	14	25 ± 9	23.6		2.5 ± 0.9	2.3	
<4 cm	20	25 ± 8	24		2.9 ± 0.8	2.8	
≥4 cm	15	26 ± 6	25.1		2.9 ± 0.8	2.8	

[a]Data are for 49 participants. Abbreviations: AUC_{0-24}, area under the concentration-time curve from 0 to 24 h; C_{max}, peak (maximum) concentration.
[b]*P* values were determined by the Wilcoxon rank-sum and Kruskal-Wallis tests. NS, not significant ($P > 0.05$).

There was a disproportionate distribution of the *SLCO1B1* c.388A>G, *SLCO1B1* c.521T>C, and *SLCO1B3* c.334T>G genotypes among races (Table 5). No significant difference in genotype data were found between laboratories.

DISCUSSION

The pharmacokinetic properties of daily (5 times/week) moxifloxacin treatment were characterized as part of this substudy of 2-month trials of rifampin-based, multidrug intensive-phase treatment for drug-sensitive tuberculosis. The moxifloxacin exposure and peak concentrations achieved when it was coadministered with rifampin were similar between participants from Africa (Uganda and South Africa) and the United States. The values of these pharmacokinetic parameters were similar to those of the moxifloxacin pharmacokinetic parameters at steady state previously reported from 16 patients with tuberculosis from the Netherlands treated with daily moxifloxacin coadministered with rifampin as a component of multidrug therapy (15), but the values for the parameters were lower than those for patients from Indonesia with tuberculosis treated with the same daily moxifloxacin dose that was coadministered with rifampin administered 3 times per week (16). Similar to the findings of other studies, the moxifloxacin AUC_{0-24} and C_{max} in our study of participants with tuberculosis were 29% to 30% lower than the moxifloxacin AUC_{0-24} and C_{max} observed in healthy volunteers who had been coadministered moxifloxacin and rifampin daily at the same study doses (17). In this study, moxifloxacin exposure or the peak concentration adjusted for weight was not associated with the rifampin AUC_{0-24}. Factors that likely affected this lack of association were the study sample size and the limited range of rifampin exposures.

TABLE 4 Relation between human single-nucleotide polymorphisms and moxifloxacin pharmacokinetic parameters in study participants[a]

				AUC_{0-24}				C_{max}			
Accession no.	Variant	Genotype	No. of participants	Median (IQR) AUC_{0-24} (μg · h/ml) by genotype	Adjusted effect (95% CI)[b]	P[c]	FDR	Median (IQR) C_{max} (μg/ml) by genotype	Adjusted effect (95% CI)[b]	P[c]	FDR
rs4149015	*SLCO1B1* g.−11187G>A	GG	45	23.6 (20.6, 27.3)	0.34 (0.11, 0.57)	≤0.005	0.037	2.7 (2.0, 3.3)	0.96 (0.25, 1.67)	≤0.009	0.06
		AG	4	34.4 (31.2, 38.8)				3.5 (3.1, 4.2)			
rs59502379	*SLCO1B1* c.1463G>C	GG	46	24.5 (21.4, 28.6)	−0.2 (−0.48, 0.08)	NS	0.53	2.7 (2.2, 3.4)	−0.28 (−1.15, 0.6)	NS	0.62
		CG	3	19.8 (17.8, 25.8)				3.0 (2.2, 3.2)			
rs2306283	*SLCO1B1* c.388A>G	GG	26	24.8 (22.9, 29.5)	−0.04 (−0.13, 0.06)	NS	0.75	3.0 (2.5, 3.4)	−0.03 (−0.33, 0.27)	NS	0.84
		GA	16	24.0 (18.5, 29.1)				2.3 (1.9, 3.1)			
		AA	7	20.7 (20.1, 23.8)				2.7 (2.2, 3.5)			
rs11045819	*SLCO1B1* c.463C>A	CC	41	24.5 (20.6, 28.6)	0.07 (−0.13, 0.26)	NS	0.75	2.7 (2.0, 3.5)	0.27 (−0.3, 0.84)	NS	0.6
		AC	8	24.3 (23.3, 28.2)				2.7 (2.3, 3.3)			
rs4149056	*SLCO1B1* c.521T>C	TT	44	24.5 (21.2, 28.8)	−0.07 (−0.3, 0.16)	NS	0.75	2.7 (2.2, 3.3)	0.27 (−0.42, 0.96)	NS	0.61
		CT	5	22.0 (20.7, 28.4)				3.4 (2.3, 3.5)			
rs4149117	*SLCO1B3* c.334T>G	GT	23	24.5 (20.2, 29.0)	0.02 (−0.08, 0.12)	NS	0.83	2.9 (2.2, 3.2)	0.21 (−0.1, 0.51)	NS	0.41
		GG	13	23.2 (20.3, 25.4)				2.7 (2.0, 3.5)			
		TT	13	26.9 (22.8, 31.8)				2.7 (2.3, 3.5)			
rs1045642	*ABCB1* (*MDR1*) c.3435C>T	CC	38	24.5 (21.7, 28.6)	0 (−0.13, 0.13)	NS	0.98	2.7 (2.1, 3.3)	0.31 (−0.08, 0.69)	NS	0.41
		CT	9	20.7 (18.6, 24.8)				2.4 (2.2, 3.1)			
		TT	2	30.1 (26.7, 33.6)				3.8 (3.7, 3.9)			

[a]Data are for 49 participants. Abbreviations: AUC_{0-24}, area under the concentration-time curve from 0 to 24 h; IQR, interquartile range; CI, confidence interval; C_{max}, peak (maximum) concentration; FDR, false discovery rate.

[b]Moxifloxacin AUC_{0-24} adjusted for weight and gender and C_{max} adjusted for weight alone with the BIC model. Effects were adjusted for the average difference in the ln AUC_{0-24} or C_{max} due to an increase of 1 in the minor allele.

[c]*P* values were determined by analysis of covariance. NS, not significant ($P > 0.05$).

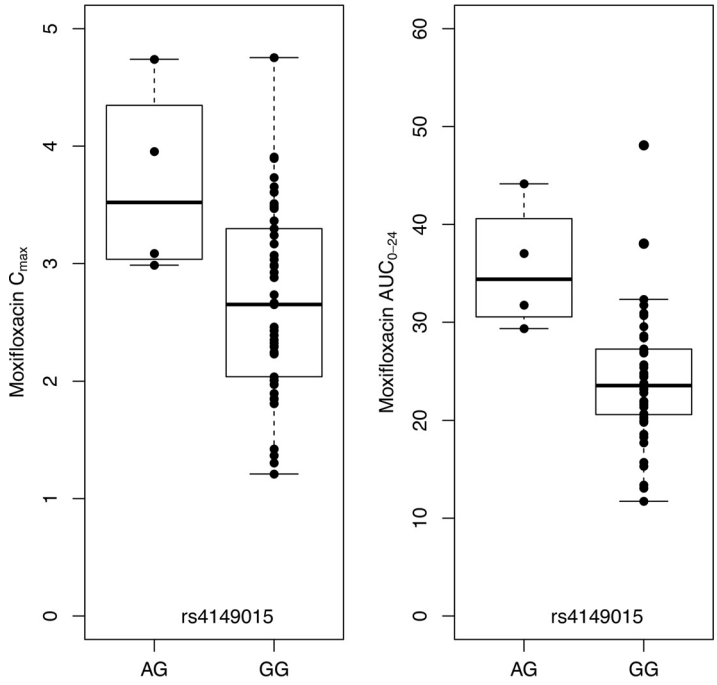

FIG 1 Relations between the *SLCO1B1* g.−11187G>A polymorphism (rs409015) and the moxifloxacin C_{max} and AUC_{0-24} among participants in Tuberculosis Trials Consortium pharmacokinetic studies 27 and 28. The pharmacokinetic data were not adjusted for covariates.

Moderate interindividual variability of the moxifloxacin AUC_{0-24} and C_{max} was observed in this study.

A new finding in this study is the polymorphism for a human drug transporter associated with moxifloxacin exposure and/or the moxifloxacin peak concentration. The moxifloxacin peak concentration and exposure were significantly greater in both the unadjusted and model-adjusted analyses in participants who had the AG genotype at *SLCO1B1* g.−11187 than in participants who had the GG genotype. Because of the absence of participants with the AA genotype, the mode of inheritance (e.g., dominant,

TABLE 5 Distribution of single-nucleotide polymorphisms among races or regions for the 49 study participants

			Race			Region		
Accession no.	Variant	Genotype	No. (%) black	No. (%) white	*P*[a]	No. (%) from Africa	No. (%) not from Africa	*P*
			29 (100)	20 (100)		26 (100)	23 (100)	
rs4149015	*SLCO1B1* g.−11187G>A	GG	28 (97)	17 (85)	0.36	25 (96)	20 (87)	0.52
		AG	1 (3)	3 (15)		1 (4)	3 (13)	
rs4149117	*SLCO1B3* c.334T>G	GG	1 (3)	12 (60)	<0.001	1 (4)	12 (52)	<0.001
		GT	15 (52)	(8) 40		12 (46)	11 (48)	
		TT	13 (45)	0 (0)		13 (50)	0 (0)	
rs2306283	*SLCO1B1* c.388A>G	CC	22 (76)	4 (20)	<0.001	21 (81)	5 (22)	<0.001
		CT	7 (24)	9 (45)		5 (19)	11 (48)	
		TT	0 (0)	7 (35)		0 (0)	7 (30)	
rs4149056	*SLCO1B1* c.521T>C	TT	29 (100)	15 (75)	0.02	26 (100)	18 (78)	0.04
		CT	0 (0)	5 (25)		0 (0)	5 (22)	
rs1045642	*ABCB1* (*MDR1*) c.3435C>T	CC	25 (86)	13 (65)	0.11	23 (88)	15 (65)	0.10
		CT	4 (14)	5 (25)		3 (12)	6 (26)	
		TT	0 (0)	2 (10)		0 (0.0)	2 (9)	
rs59502379	*SLCO1B1* c.1463G>C	GG	26 (90)	20 (100)	0.38	23 (88)	23 (100)	0.28
		CG	3 (10)	0 (0)		3 (12)	0 (0)	
rs11045819	*SLCO1B1* c.463C>A	CC	23 (79)	18 (90)	0.55	21 (81)	20 (87)	0.84
		AC	6 (21)	2 (10)		5 (19)	3 (13)	

[a]*P* values were determined by the chi-square test.

recessive, or additive) could not be assessed. Peptide products of the *SLCO* genes mediate the transport of xenobiotics in the gastrointestinal tract and liver. A decrease in the transporter peptide activity encoded by *SLCO1B1*, which is located at the interface of the portal circulation and the hepatocyte, could result in reduced hepatic uptake (affecting drug metabolism and/or excretion by the liver) and an increase in systemic drug exposure. This pathway has been used to explain the pharmacokinetic association of the *SLCO1B1* polymorphism with elevated atorvastatin and pravastatin concentrations (18, 19) and is consistent with the effect of the *SLCO1B1* g.−11187G>A polymorphism on moxifloxacin concentrations in this study. The *SLCO1B1* g.−11187G>A polymorphism and the participants' race or region of enrollment were not associated (Table 5). The SNP of the transporter *ABCB1* (*MDR1*) c.3435C>T (rs1045642) was not associated with the moxifloxacin C_{max} or AUC among 16 healthy adults in an earlier single-site study of the effects of rifampin and gene polymorphisms on plasma moxifloxacin concentrations (17). Our current study of 49 other participants with tuberculosis from different geographical regions also did not detect an association between the *ABCB1* c.3435C>T polymorphism and the moxifloxacin C_{max} or AUC.

A limitation of the present study is that only transporter genes were evaluated. Moxifloxacin undergoes phase II biotransformation by sulfate conjugation, with the resultant M1 metabolite accounting for 38% of an oral dose of moxifloxacin, and glucuronide conjugation, with the resultant M2 metabolite accounting for 14% of an oral dose (12). Both moxifloxacin metabolites M1 and M2 are reported to be pharmacologically inactive (12). Members of the UDP-glucuronosyltransferase family of enzymes metabolize various drugs, and the gene *UGT1A1* encodes an UDP-glucuronosyltransferase that metabolizes moxifloxacin. The SNP *UGT1A1*28* is associated with the disposition and toxicity of the drug irinotecan, a topoisomerase I inhibitor used for the treatment of colorectal cancer (20). Hasunuma et al. found that polymorphisms of both *UGT1A1*6* and *UGT1A1*28* were not significantly associated with changes in the moxifloxacin AUC from 0 h to infinity or C_{max} among 79 healthy volunteers of different ethnicities (21). However, other SNPs responsible for glucuronidation (22–24) or sulfate conjugation could potentially be associated with changes in the moxifloxacin C_{max} and/or exposure.

Because of its bactericidal activity, moxifloxacin at 400 mg was evaluated as a component in multidrug regimens of two phase 3 treatment-shortening trials of tuberculosis (4, 5). However, the moxifloxacin treatment arms in each of these trials failed to show noninferiority compared to standard therapy. Preclinical studies suggested that the pharmacodynamic parameter that best described the *in vivo* efficacy of moxifloxacin was the ratio of the moxifloxacin AUC to the MIC (21, 22). However, to achieve target AUC/MIC ratios, an estimated moxifloxacin AUC of >50 μg · h/ml would be needed. Many patients do not achieve the target exposure with administration of a 400-mg daily dose of moxifloxacin. Pharmacokinetic and pharmacodynamic *in vitro* modeling suggested that greater bactericidal activity likely could be achieved in many more patients with moxifloxacin daily doses of up to 800 mg (24–26). However, before the routine clinical use of higher daily doses, evaluation of the safety and tolerability of moxifloxacin doses of >400 mg daily is needed (27).

Moxifloxacin has a favorable safety profile when used as monotherapy at 400 mg daily for the treatment of pneumonia according to labeling guidelines approved by the United States Food and Drug Administration (FDA) (28). In a systemic review and meta-analysis, Liu and colleagues reported that although the absolute risk was small, in subgroup analyses the relative risk (RR) of cardiac arrhythmia was increased with moxifloxacin use (RR, 4.20; 95% confidence interval, 1.91 to 9.27; $P < 0.001$) (29). The FDA warns that the arrhythmia risk increases with QT/QTc interval prolongation; i.e., increases of the mean QT/QTc interval of between 10 and 20 ms could be of clinical importance, and a mean increase of >20 ms has a substantially increased probability of being proarrhythmic (30). Panicker and colleagues modeled the moxifloxacin exposure-response in healthy participants with intensive electrocardiogram analyses to

estimate the relation of the moxifloxacin concentration to ΔΔQTcF (Fridericia's formula to adjust for the physiologic shortening of the QT interval that occurs as the heart rate increases, permitting comparison of the QT interval across a range of rates) (31). In 46 healthy participants, the slope of the concentration-QTc curve was 4.12 ms of ΔΔQTcF per μg/ml, and for the mean C_{max} of 2.95 μg/ml among study participants, the estimated ΔΔQTcF was 13.4 ms (90% confidence interval, 11.3 to 15.4 ms). In our study, the estimated moxifloxacin C_{max} in four participants with the *SLCO1B1* g.−11187GA genotype ranged from 2.98 to 4.74 μg/ml. The FDA cautions that moxifloxacin should be avoided in patients who have a prolonged baseline QT interval or who are also being treated with class IA or III antiarrhythmic medications, such as quinidine, procainamide, and amiodarone (30). A number of other drugs are associated with prolonged QTc intervals (32). Antibiotics that are recommended for the treatment of multidrug-resistant TB, in addition to fluoroquinolones, and that are associated with a prolonged QTc interval include bedaquiline, delamanid, and clofazimine. The safety of coadministration of moxifloxacin with any of these other drugs used to treat multidrug-resistant TB requires further clinical evaluation (33, 34). Additionally, the present study suggests that the *SLCO1B1* g.−11187GA genotype possibly increased the risk of a prolonged QTc interval.

A limitation of the present study is that we did not compare plasma moxifloxacin concentrations and QTc intervals, because QTc interval measurements were not evaluated in the study participants during treatment. However, the concentration-dependent prolongation of QTc intervals during moxifloxacin therapy is well established (9, 10, 35, 36). Another limitation of the study is that the AG genotype was identified in only 4 of 49 participants for whom moxifloxacin pharmacokinetics were determined and genomic analyses of *SLCO1B1* g.−11187G>A were performed. However, in the larger group of 72 participants in studies 27 and 28 with genomic analysis of *SLCO1B1* g.−11187G>A, 8 (11%) had the AG genotype. Because the African study participants were predominately from Uganda and the non-African participants were from the United States, further study is needed to characterize the prevalence of *SLCO1B1* g.−11187G>A among other populations. The strengths of this pharmacokinetic study include the comparisons of well-characterized participants who had culture-confirmed pulmonary TB and who were receiving directly supervised therapy during carefully conducted clinical trials, enrollment of participants from 2 continents, and the use of pharmacokinetic sampling at 7 times to capture complete pharmacokinetic data for the study subjects.

This study is the first to describe an association of an elevated plasma moxifloxacin C_{max} and exposure with a drug transporter, identified as the *SLCO1B1* g.−11187A>G genotype. Because moxifloxacin exhibits concentration-dependent prolongation of human QTc intervals and a prolonged QTc interval is associated with cardiac arrhythmias, the present results support recommendations for baseline electrocardiographic tests and careful monitoring of QTc intervals during therapy when moxifloxacin is coadministered with other drugs that may additively prolong QTc intervals, as can occur in the treatment of multidrug-resistant TB. Further study is needed to evaluate the risk for the prolongation of QTc intervals associated with the *SLCO1B1* g.−11187G>A variant.

MATERIALS AND METHODS

Experimental design. Participants were recruited as a convenience sample to this pharmacogenomic substudy from Tuberculosis Trials Consortium (TBTC) pharmacokinetic studies 27 and 28. Both trials were prospective, placebo-controlled, randomized phase 2 studies conducted during the first 2 months of intensive-phase TB treatment. Study 27 compared moxifloxacin to ethambutol (coadministered with isoniazid, rifampin, and pyrazinamide) administered 5 versus 3 times per week (37). Study 28 compared moxifloxacin to isoniazid (with rifampin, pyrazinamide, and ethambutol) administered 5 times per week (38). All participants were adults with newly diagnosed, sputum smear-positive pulmonary TB. Race and ethnicity were identified by self-report by the study participants and participants were further categorized by TBTC personnel into demographic groups. The institutional review boards of the Centers for Disease Control and Prevention and the participating TBTC sites approved the study, and informed

consent was obtained from all participants. This intensive pharmacokinetic substudy was registered at ClinicalTrials.gov under registration no. NCT00164463 (39).

Sample collection. One pharmacokinetic sampling was performed after ≥9 doses of moxifloxacin (400 mg for all participants) were administered by directly observed therapy 5 days per week and after ≥3 consecutive daily doses. Before pharmacokinetic sampling, all drugs were given as fasting doses. Plasma samples were collected immediately before dosing and at 1, 2, 6, 8 to 10, 11 to 13, and 23 to 25 h after dosing. Pharmacokinetic samples were placed in an ice-water bath until centrifugation; after centrifugation, plasma aliquots were frozen at ≤−70°C within 60 min after collection.

Moxifloxacin determination. Moxifloxacin was analyzed with reverse-phase high-performance liquid chromatography and fluorescence detection (Bayer internal method report BAY 12-8039/HPLC/S/1.01; NorthEast Bioanalytical Laboratories, Hamden, CT) (17). Sample preparation included protein precipitation using acidified acetonitrile followed by dilution with buffer. The calibration range of the procedure was 0.026 to 4.0 μg/ml. On the basis of the results for the quality control samples tested during the analysis of subject samples, the interday precision was 2.2% to 4.8% and accuracy was 102.8% to 105.7%.

Genotype analyses. Genotyping of 7 SNPs of the transporter genes *SLCO1B1*, *SLCO1B3*, and *ABCB1*—*SLCO1B1* g.−11187G>A (rs4140915), *SLCO1B1* c.388A>G (rs2306283), *SLCO1B1* c.463C>A (rs11045819), *SLCO1B1* c.521T>C (rs4149056), *SLCO1B1* 1463G>C (rs59502379), *SLCO1B3* c.334T>G (rs4149117), and *ABCB1* c.3435C>T (rs1045642)—had previously been performed at the Centers for Disease Control and Prevention for the participants in the present study as part of a study of rifampin pharmacokinetics (13). Genotyping of the same 7 SNPs was repeated at the Genomics Shared Resource Facility at the University of Texas Health Science Center, San Antonio. DNA was isolated from one sample of peripheral blood leukocytes (QIAamp DNA blood kit; Qiagen Inc., Germantown, MD). The *SLCO1B1* variant g.−11187G>A (rs4149015) was genotyped with an allelic discrimination assay (TaqMan; catalog number C_32325356_10; Applied Biosystems, Thermo Fisher Scientific, Waltham, MA). DNA (10 ng) in a 10-μl PCR mixture containing reagent solution (1×; Universal master mix; Applied Biosystems, Foster City, CA) was amplified by an SNP genotyping assay using a sequence detection system (catalog number 7900HT; Applied Biosystems). Genotypes were analyzed using SDS (v2.4) software (Applied Biosystems). The genotypes for the 6 additional SNPs were determined using a high-throughput genotyping assay (VeraCode GoldenGate; Illumina Inc., San Diego, CA). A custom multiplex panel of primers for the candidate SNPs in *SLCO1B1*, *SLCO1B3*, and *ABCB1* was designed (Illumina Assay Design Tool, Illumina) and developed into an oligonucleotide pool for the genotyping assay (VeraCode GoldenGate). DNA (250 ng) was used as the template for the assay. The assay was performed in 96-well plates according to the instructions from the manufacturer (Illumina). The plates were scanned (Illumina BeadXpress reader), and genotypes were analyzed using software (GenomeStudio, Illumina).

Pharmacokinetic and statistical analyses. Analyses of the area under the concentration-time curve from 0 to 24 h (AUC_{0-24}) were performed using noncompartmental techniques (WinNonlin, v4, software; Pharsight Corporation, Mountain View, CA). Data analyses were performed with statistical software (R, v3+; R Foundation, Vienna, Austria). Demographics and clinical features were cross-tabulated by geographic region of origin (Africa versus United States) (Table 1). Associations were evaluated with the chi-square test (categorical variables) or the *t* test (continuous variables).

Moxifloxacin pharmacokinetic parameters (AUC_{0-24}, AUC_{0-24} per kilogram of body weight, peak [maximum] concentration [C_{max}], half-life) were stratified by geographic region, summarized by arithmetic and geometric means, and evaluated for significance with the nonparametric Wilcoxon rank sum test (Table 2). Moxifloxacin AUC_{0-24} and C_{max} arithmetic and geometric means were evaluated by age (tertiles), weight (tertiles), gender, geographic region of enrollment, race, human immunodeficiency virus infection status, and the presence and aggregate size of cavities on chest radiographs (prior to study enrollment) using nonparametric Wilcoxon rank-sum and Kruskal-Wallis tests (Table 3).

The median and interquartile range (IQR) of the AUC_{0-24} and peak concentration versus genotype were compared by an analysis of covariance with modeled data (Table 4). In addition, pharmacokinetic parameters were modeled using linear regression to adjust for clinical variables selected using the Bayesian information criterion (BIC) (40). Independent variables included in the model selection process using the BIC criterion included demographic factors (age [in years; tertiles], gender [male/female], and race[black/white]), clinical aspects (weight [in kilograms; tertiles] and cavities identified at the baseline chest radiograph for the treatment trial [none, <4 cm, ≥4 cm]), treatment regimen with concomitant study drugs (rifampin exposure [AUC_{0-24}], isoniazid [yes/no], and ethambutol [yes/no]), and other laboratory parameters (HIV infection status [yes/no] and aspartate aminotransferase, total bilirubin, and creatinine concentrations [continuous]). Because race and region were colinear, region alone was included in the model selection process. Weight and gender were considered simultaneously, and interactions between weight and gender were assessed for statistical significance. The moxifloxacin AUC_{0-24} was log transformed because of positive skewness, but C_{max} was analyzed untransformed because the data distribution was symmetrical and Gaussian. The additive inheritance model was used to estimate the effects of the SNP alleles. The additive inheritance model was used to estimate the effect of the SNP alleles. Each SNP was added into the model separately while adjusting for the effects of the clinical variables identified through the model selection process described above. Statistical significance was defined by a *P* value of ≤0.05. The tests of significance for multiple SNPs were adjusted using the false discovery rate (FDR).

Genotypes were cross-tabulated by race (black versus white) and geographic region of origin (Africa versus United States) by the chi-square test (Table 5).

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